

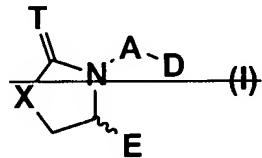
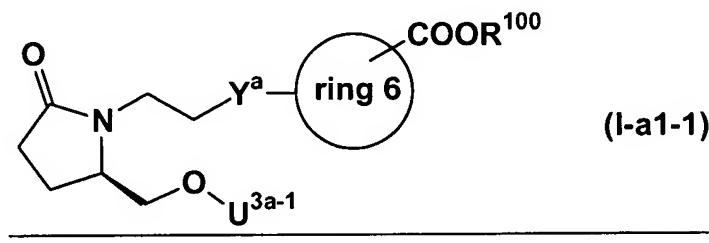
RESPONSE TO RESTRICTION REQUIREMENT AND
PRELIMINARY AMENDMENT
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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) An 8-azaprostaglandin derivative compound represented by formula (I-a1-1)



(wherein

Y^a is -S- or -SO₂-;

ring6 is 5 or 6 membered mono-heterocyclic aryl containing hetero atoms selected from 1 to 4 nitrogen, 1 to 2 oxygen, and/or 1 to 2 sulfur atoms which may be partially or fully saturated;

R¹⁰⁰ is a hydrogen atom or C1-4 alkyl;

U^{3a-1} is ring4;

ring 4 is C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated;

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~~T~~ is (1) an oxygen atom or (2) a sulfur atom;

~~X~~ is (1) CH_2 , (2) O or (3) S;

~~A~~ is A^+ or A^2 ;

~~A¹~~ is (1) C2-8 straight chain alkylene optionally substituted by 1 to 2 C1-4 alkyl(s),
(2) C2-8 straight chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl(s) or (3) C2-8
straight chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl(s);

~~A²~~ is $\text{G}^+ \text{G}^2 \text{G}^3$;

~~G¹~~ is (1) C1-4 straight chain alkylene optionally substituted by 1 to 2 C1-4 alkyl(s),
(2) C2-4 straight chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl(s) or (3) C2-4
straight chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl(s);

~~G²~~ is (1) Y, (2) ring1, (3) Y ring1, (4) ring1 Y or (5) Y-C1-4 alkylene ring1;

~~Y~~ is (1) S, (2) SO, (3) SO_2 , (4) O or (5) NR^+ ;

~~R¹~~ is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl;

~~G³~~ is (1) a bond, (2) C1-4 straight chain alkylene optionally substituted by 1 to 2 C1-4 alkyl(s),
(3) C2-4 straight chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl(s) or (4)
C2-4 straight chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl(s);

~~D~~ is D^+ or D^2 ;

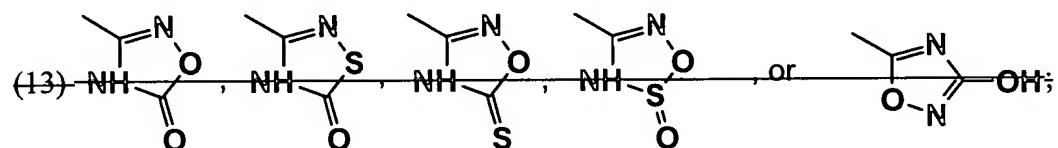
~~D¹~~ is (1) COOH, (2) COOR², (3) tetrazol-5-yl or (4) CONR³SO₂R⁴;

~~R²~~ is (1) C1-10 alkyl, (2) phenyl, (3) C1-10 alkyl substituted by phenyl or (4)
biphenyl;

~~R³~~ is (1) a hydrogen atom or (2) C1-10 alkyl;

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~~R⁴ is (1) C1-10 alkyl or (2) phenyl;~~
~~D² is (1) CH₂OH, (2) CH₂OR⁵, (3) hydroxy, (4) OR⁵, (5) formyl, (6) CONR⁶R⁷,~~
~~(7) CONR⁶SO₂R⁸, (8) CO (NH amino acid residue CO)_mOH, (9) O (CO amino acid residue-~~
~~NH)_mH, (10) COOR⁹, (11) OCO-R¹⁰, (12) COO-Z¹-Z²-Z³, or~~



~~R⁵ is C1-10 alkyl;~~
~~R⁶ and R⁷ are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;~~
~~R⁸ is C1-10 alkyl substituted by phenyl;~~
~~R⁹ is (1) C1-10 alkyl substituted by biphenyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy and halogen or (2) biphenyl substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy and halogen atom;~~
~~R¹⁰ is (1) phenyl or (2) C1-10 alkyl;~~
~~m is 1 or 2;~~
~~Z¹ is (1) C1-15 alkylene, (2) C2-15 alkenylene or (3) C2-15 alkynylene;~~
~~Z² is (1) CO, (2) OCO, (3) COO, (4) CONR^{Z4}, (5) NR^{Z2}CO, (6) O, (7) S,~~
~~(8) SO₂, (9) SO₂NR^{Z2}, (10) NR^{Z2}SO₂, (11) NR^{Z3}, (12) NR^{Z4}CONR^{Z5}, (13) NR^{Z6}COO,~~
~~(14) OCONR^{Z7} or (15) OC(O)O;~~

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~~Z³ is (1) a hydrogen atom, (2) C1-15 alkyl, (3) C2-15 alkenyl, (4) C2-15 alkynyl, (5) ringZ or (6) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl NR^{Z8} or ringZ;~~

~~ringZ is (1) C3-15 mono-, bi- or tri-carboyclic aryl which may be partially or fully saturated or (2) 3- to 15-membered mono-, bi- or tri-heterocyclic aryl which may be partially or fully saturated and contains 1 to 4 hetero atom(s) selected from oxygen, nitrogen and sulfur atom(s);~~

~~R^{Z1}, R^{Z2}, R^{Z3}, R^{Z4}, R^{Z5}, R^{Z6}, R^{Z7} and R^{Z8} are, each independently, a hydrogen atom or C1-15 alkyl;~~

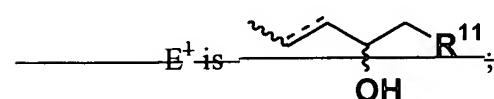
~~R^{Z1} and Z³ may be taken together with the nitrogen atom to which they are attached to form a 5- to 7-membered saturated mono-heterocyclic ring, and the heterocyclic ring may contain other one hetero atom selected from oxygen, nitrogen and sulfur atoms;~~

~~ringZ and the saturated mono-heterocyclic ring formed by R^{Z1}, Z³ and the nitrogen atom to which they are attached may be substituted by 1-3 groups selected from following (1) to (4):~~

~~(1) C1-15 alkyl, (2) C2-15 alkenyl, (3) C2-15 alkynyl, (4) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio or C1-10 alkyl NR^{Z9};~~

~~R^{Z9} is a hydrogen atom or C1-10 alkyl;~~

~~E is E¹ or E²;~~



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~~R¹¹ is (1) C1-10 alkyl, (2) C1-10 alkylthio, (3) C1-10 alkyl substituted by C3-8 cycloalkyl, (4) C1-10 alkyl substituted by ring2 or (5) C1-10 alkyl substituted by W¹-W²-ring2;~~

~~W¹ is (1) O, (2) S, (3) SO, (4) SO₂, (5) NR¹¹⁺¹, (6) carbonyl, (7) NR¹¹⁺¹SO₂, (8) carbonyl amine or (9) aminocarbonyl;~~

~~R¹¹⁺¹ is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl;~~

~~W² is (1) a bond or (2) C1-8 alkyl optionally substituted by C1-4 alkyl, halogen or hydroxy;~~

~~E² is (1) U¹-U²-U³ or (2) ring4;~~

~~U¹ is (1) C1-4 alkylene, (2) C2-4 alkenylene, (3) C2-4 alkynylene, (4) ring3, (5) C1-4 alkylene ring3, (6) C2-4 alkenylene ring3 or (7) C2-4 alkynylene ring3;~~

~~U² is (1) a bond, (2) CH₂, (3) CHOH, (4) O, (5) S, (6) SO, (7) SO₂, (8) NR¹², (9) carbonyl, (10) NR¹²SO₂, (11) carbonyl amine or (12) aminocarbonyl;~~

~~R¹² is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl;~~

~~U³ is (1) C1-8 alkyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and NR¹³R¹⁴, (2) C2-8 alkenyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and NR¹³R¹⁴, (3) C2-8 alkynyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and NR¹³R¹⁴, (4) C1-8 alkyl substituted by ring4 or (5) ring4;~~

~~R¹³ and R¹⁴ are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;~~

~~ring1, ring2, ring3 or ring4 may be substituted by 1 to 5 R;~~

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R is (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkylthio, (6) halogen, (7) hydroxy, (8) nitro, (9) -NR¹⁵R¹⁶, (10) C1-10 alkyl substituted by C1-10 alkoxy, (11) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (12) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s), (13) C1-10 alkyl substituted by -NR¹⁵R¹⁶, (14) ring5, (15) -O-ring5, (16) C1-10 alkyl substituted by ring5, (17) C2-10 alkenyl substituted by ring5, (18) C2-10 alkynyl substituted by ring5, (19) C1-10 alkoxy substituted by ring5, (20) C1-10 alkyl substituted by -O-ring5, (21) COOR¹⁷, (22) C1-10 alkoxy substituted by 1 to 4 halogen atom(s), (23) formyl, (24) C1-10 alkyl substituted by hydroxy or (25) C2-10 acyl;

R¹⁵, R¹⁶ and R¹⁷ are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;

~~ring5 may be substituted by 1 to 3 substituent(s) selected from following (1)-(9):~~

~~(1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkyl substituted by C1-10 alkoxy, (6) halogen atom, (7) hydroxy, (8) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (9) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s);~~

~~ring1, ring2, ring3, ring4 and ring5 is are, each independently,~~

(1) C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or (2) 3- to 15-membered mono-, bi- or tri-heterocyclic aryl which may be partially or fully saturated and contains a hetero atom(s) selected from 1 to 4 nitrogen, 1 to 2 oxygen and/or 1 to 2 sulfur atom(s);

~~ring5 may be substituted by 1 to 3 substituent(s) selected from following (1)-(9):~~

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(1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkyl substituted by C1-10 alkoxy, (6) halogen atom, (7) hydroxy, (8) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (9) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s); and

wherein

- 1) when E is E^2 , E^2 is $U^1-U^2-U^3$, and U^1 is C2 alkylene or C2 alkenylene, U^2 is not $CHOH$,
- 2) when U^3 is C1-8 alkyl substituted by at least one hydroxy, U^1-U^2 is not C2 alkylene or C2 alkenylene;
- 3) when A is A^+ and D is D^+ , then E is not E^+ ;
- 4) when T is oxygen atom, X is CH_2 , D is D^+ , D^+ is $COOH$, A is A^+ , A^+ is C2-8 straight chain alkylene, E is E^2 , E^2 is $U^1-U^2-U^3$, U^1 is C1-4 alkylene and U^3 is C1-8 alkyl, then U^2 is not a bond, CH_2 , NR^{12} or carbonyl,
- 5) when T is an oxygen atom, X is CH_2 , D is D^+ , D^+ is $COOH$, A is A^2 , G^+ is C1-4 alkylene, G^2 is O or NR^+ , G^3 is a bond or C1-4 alkylene, E is E^2 , E^2 is $U^1-U^2-U^3$, U^1 is C1-4 alkylene and U^3 is C1-8 alkyl, the U^2 is not a bond, CH_2 , NR^{12} or carbonyl,
- 6) when T is an oxygen atom, X is CH_2 , D is D^+ , E is E^2 , E^2 is $U^1-U^2-U^3$, U^1 is C2 alkylene or C2 alkenylene and U^2 is CO, then A is not A^+ ,
- 7) 4 [(2 ((2R)-2 [(1E,3S)-3 hydroxy oct-1-enyl] 5 oxo pyrrolidin-1-yl)ethyl)thio]butanoic acid and 4 (2 [(R)-2 ((E)-3 hydroxy oct-1-enyl) 5 oxo pyrrolidin-1-yl] ethyl)benzoic acid are excluded,

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a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

Claims 2.-17. (canceled).

18. (Previously Presented) A pharmaceutical composition, which comprises the 8-azaprostaglandin derivative compound according to claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof and a pharmaceutical acceptable carrier.

19. (Original) The pharmaceutical composition according to claim 18, which is EP₂ and/or EP₄ receptor agonist.

20. (Currently Amended) A method for preventing and/or treating ~~immune diseases, allergic diseases, neuronal cell death, dysmenorrheal, premature birth, abortion, baldness, retinal neuropathy, erectile dysfunction, arthritis, pulmonary injury, pulmonary fibrosis, pulmonary emphysema, bronchitis, chronic obstructive pulmonary disease, hepatic injury, acute hepatitis, liver cirrhosis, shock, nephritis, renal failure, circulatory diseases, systemic inflammatory response syndrome, sepsis, hemophagocytosis syndrome, macrophage activation syndrome, still disease, Kawasaki Disease, burn, systemic granuloma, ulcerative colitis, Crohn disease, hyperecytokinemia at dialysis, multiple organ failure, or bone diseases~~, which comprises administering the 8-azaprostaglandin derivative compound according to claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

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21. (New) The 8-azaprostaglandin derivative compound according to claim 1, which is selected from the group consisting of:

14-oxa-14-(3,5-dichlorophenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(4-nitro-3-methylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(3-nitro-2-methylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(3-nitro-4-methylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(2-fluoro-3-trifluoromethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(3,4,5-trimethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(5,6,7,8-tetrahydronaphthalen-1-yl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(2-chloro-3-trifluoromethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

14-oxa-14-(3-chloro-4-fluorophenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;

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14-oxa-14-(3-trifluoromethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;
14-oxa-14-(3-trifluoromethoxyphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;
14-oxa-14-(4-chloro-3-ethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;
14-oxa-14-(4-methylindan-7-yl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;
14-oxa-14-(4-chloro-3-trifluoromethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate;
14-oxa-14-(4-chloro-3,5-dimethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate; and
14-oxa-14-(4-fluoro-3-trifluoromethylphenyl)-5-(4-carboxythiazol-2-yl)-9-oxo-
1,2,3,4,15,16,17,18,19,20-decanor-5-thia-8-azaprostanate; or
the pharmaceutically acceptable salt thereof or the cyclodextrin clathrate thereof.